REMARKS

In a final Office Action dated March 20, 2008, the Examiner rejected Claims 1 and 4-17 under 35 U.S.C. §§ 101, 103 and 112.

Applicants address the Examiner's rejections below. In view of the amendments above and remarks herein, Applicants respectfully request reconsideration of the merits of this application. Accordingly, Applicants respectfully request that a timely notice of allowance be issued in this case.

Telephonic Interview

Inventor Tocchini-Valentini and his representatives thank Examiner Shin and her supervisor, Jon Eric Angell, for their time during a telephonic interview on July 23, 2008. During the interview, the parties discussed the outstanding obviousness rejection. Although an agreement was not reached, the discussion was fruitful, particularly in identifying differences between the claimed methods and the methods disclosed in the art. Examiner Shin indicated that Inventor Tocchini-Valentini's comments on the differences between the claimed methods and the art maybe helpful in establishing that the inventors had no reasonable expectation of success in using trans-formed structures over the cis-formed structures shown in the art. Applicants' summary of the interview is consistent with the Examiner's Summary mailed July 29, 2008.

Rejection Under 35 U.S.C. § 101

The Examiner rejected Claims 1 and 4-17 as claiming the same invention as Claims 1-17 of US Patent Application No. 10/296,574. A response to a final Office Action was due February 29, 2008, for US Patent Application No. 10/296,574. Applicants believe that US Patent Application No. 10/296,574 is now abandon because a timely response was not submitted to the Office. In view of the abandonment of US Patent Application No. 10/296,574, Applicants respectfully request reconsideration of this rejection as applied to Claims 1 and 4-17.

Rejections Under 35 U.S.C. § 103

The Examiner maintained a rejection of Claims 1 and 4-17 as obvious over Fabbri S, *et al.*, "Conservation of substrate recognition mechanisms by tRNA splicing endonucleases," Science 280:284-286 (1998) in view of Santoro S & Joyce G, "A general purpose RNA-cleaving

DNA enzyme," Proc. Natl. Acad. Sci. USA 94:4262-4266 (1997). The Examiner alleged that it would have been obvious to one of one or ordinary skill in the art to use a conserved, common mechanism for recognizing non-tRNA RNA substrates having a BHB motif to cleave a desired target nucleic acid after reading Fabbri *et al.* and Santoro & Joyce. 66 (1997). Applicants respectfully disagree.

With respect to Claims 1-11, Applicants acknowledge that Fabbri *et al.* disclosed that pre-tRNAs (*i.e.*, a tRNA structure having (1) a 5'-terminal phosphate group; (2) an acceptor stem comprising a seven base pair stem made by the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides; (3) a CCA tail at the 3' end; (4) a D loop comprising a four base pair stem ending in a loop; (5) an anticodon loop comprising a five base pair stem whose loop contains the anticodon; and (6) a T loop comprising a five base pair stem) and mini-substrates having whole, cis-formed BHB motif (including a terminal loop) can be cleaved by not only archaeal endonucleases, but also by eukaryal tRNA endonucleases (*see*, FIGS. 1-2 of Fabbri *et al.*). However, and as discussed in the interview, Fabbri *et al.* did not contemplate or disclose to one of ordinary skill in the art that a trans-formed BHB motif (lacking a terminal loop) could be cleaved by eukaryal tRNA endonucleases (*see, e.g.*, FIGS. 4 and 13 of the application for trans-formed BHBs). Thus, in contrast to Fabbri *et al.*, the claimed methods do not require all the structures present in pre-tRNA for cleavage, which allows one to advantageously cleave non-tRNA molecules.

The Examiner alleged that Fabbri *et al.* disclosed to one of ordinary skill in the art that he or she can trigger target RNA cleavage simply by introducing an oligonucleotide that has the appropriate motif (*see*, last paragraph on p. 285). Applicants respectfully disagree with the Examiner's characterization of Fabbri *et al.* and submit a Declaration by Inventor Tocchini-Valentini in support of their position. As Dr. Tocchini-Valentini explains, he was the main author of Fabbri *et al.* and personally wrote the paragraph referenced by Examiner Shin. Dr. Tocchini-Valentini further explains that the referenced paragraph, as well as the remainder of Fabbri *et al.*, was strictly directed toward cleavage of pre-tRNAs and mini-substrates having a whole, cis-formed BHB motif and that Fabbri *et al.* did not contemplate or disclose trans-formed BHBs. It was neither known, nor predictable, at the time of Fabbri *et al.* that a trans-formed BHB could result in cleavage of an RNA molecule by eukaryal tRNA endonucleases. In fact, Dr. Tocchini Valentini indicates more than three years passed after Fabbri *et al.* before his group

considered trans-formed structures and non-tRNA molecules as substrates for eukaryal endonucleases (*see*, Fruscoloni P, *et al.*, "Cleavage of non-tRNA substrates by eukaryal tRNA splicing endonucleases," EMBO Rep. 2:217-221 (2001); cited in Supplemental IDS). That work was described in corresponding US Patent Application No. 10/296,574 (now abandoned in favor of this application), to which this application claims benefit to. In contrast, the claimed methods are directed toward Applicants' surprising finding that such enzymes can recognize and cleave trans-formed structures having only a BHB motif.

With respect to Santoro & Joyce, Applicants reiterate remarks presented in previous responses. Briefly, Santoro & Joyce disclosed DNAzymes, which are catalytic nucleic acids. Catalytic nucleic acids are not structurally the same as eukaryal tRNA endonucleases, as the former are made of amino acids. As Dr. Tocchini-Valentini opines, Santoro & Joyce are therefore not applicable to the claimed methods because Watson-Crick base-pairing, which is required by DNAzymes, is not used by eukaryal tRNA endonucleases for substrate recognition. In other words, Watson-Crick base pairing is not enough to cause recognition and cleavage by eukaryal tRNA endonucleases.

Because neither Fabbri *et al.* nor Santoro & Joyce contemplated or disclosed that trans-formed BHBs alone are sufficient to result in cleavage of a RNA substrate by eukaryal tRNA endonucleases, they cannot render the claimed methods obvious. In view of the Declaration and the remarks presented herein, Applicants respectfully request reconsideration of this rejection as applied to Claims 1-11.

With respect to Claims 12-17, neither citation contemplated or disclosed that one of ordinary skill in the art could use archaeal tRNA endonucleases to create fusion proteins in heterologous systems. Fabbri *et al.* only disclosed cleavage of pre-tRNA by tRNA endonucleases in *in vitro* conditions that did not involve cells. In contrast, the application discloses that one of ordinary skill in the art can obtain a chimeric RNA molecule with archaeal tRNA endonucleases that can be translated into a fusion protein. *See*, *e.g.*, FIGS. 4-7 of the application. Applicants were the first to appreciate that heterologous archaeal tRNA endonucleases could cleave target RNA, and then an endogenous ligase could subsequently ligate cleavage products from the target RNA and a second RNA to produce a fusion RNA having at least one cleavage product from the first target RNA molecule and at least one cleavage product from the second target RNA molecule. This link was previously unknown in

the art; therefore, Applicants are entitled such a claim. In view of the Declaration and the remarks presented herein, Applicants respectfully request reconsideration of this rejection as applied to Claims 12-17.

Rejection under 35 U.S.C. § 112

The Examiner rejected Claims 12 and 14 under 35 U.S.C. § 112, second paragraph, for omitting essential elements. The Examiner alleged that each claims references a "second" RNA molecule, but fails to specifically refer to what is the "first" RNA molecule. Applicants amend Claims 12 and 14 so that each refers not only to a second RNA molecule, but also to a first RNA molecule. In view of this amendment, Applicants respectfully request reconsideration of this rejection.

The Examiner then rejected Claims 1 and 4-17 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. The Examiner alleged that the claims now require "one bulge of the bulge-helix-bulge has a guanine/adenine dinucleotide and the other bulge of the bulge-helix-bulge has either an uracil/adenine dinucleotide or a thymine/adenine dinucleotide," but that Applicants did not provide support for this phrase. As noted in Applicants' previous response, support for this phrase is located in, *e.g.*, FIGS. 1(4), 5, 8, 14A of the application. Each of these figures shows the cleavage sites and the dinucleotides cleaved in each bulge of the BHB. However, because RNA does not contain thymine, Applicants delete references to thymine/adenine dinucleotides in Claims 1 and 12. In view of this support, Applicants respectfully request reconsideration of this rejection.

Fees

Please charge a fee for a Request for Continued Examination under 37 C.F.R. § 1.17(e) to Deposit Account No. 17-0055.

In addition, a petition for a two-month extension of time accompanies this response so that it will be deemed to have been timely filed. No other extension of time is believed due; however, if any additional extension is due, in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to Deposit Account No. 17-0055. Likewise, no other fee is believed due in connection with this

submission. However, if a fee is due, in this or any subsequent response, please charge the fee to Deposit Account No. 17-0055.

Respectfully submitted,

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